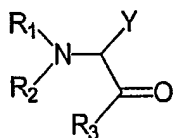


Claims

- 1 A method of increasing the sensitivity of a bacterial strain to a cell-wall active antimicrobial agents, to which the bacterial strain or a progenitor strain from which the bacterial strain has evolved is sensitive, said method comprising the step of exposing said bacterial strain to a
5 transforming agent having the following formula (I):-



Formula I

where

- moieties R_1 and R_2 are each independently selected from, alkyl, alkyloxy, alkyloxycarbonyl, alkylcarbonyloxy, alkenyl, alkenyloxy, alkenyloxycarbonyl, alkenylcarbonyloxy, alkynyl, 10 alkynyloxy, alkynyloxycarbonyl, alkynylcarbonyloxy, each of which may be substituted or unsubstituted, straight chain or branched or cyclic, aryl, aryloxy, aryloxycarbonyl, arylcarbonyloxy, each of which may be substituted or unsubstituted, and cabamoyl,
- 15 moiety R_3 is selected from alkyl, alkyloxy, alkylcarbonyloxy, alkenyl, alkenyloxy, alkenylcarbonyloxy, alkynyl, alkynyloxy, alkynylcarbonyloxy, each of which may be substituted or unsubstituted, straight chain or branched or cyclic, aryl, aryloxy, arylcarbonyloxy, each of which may be substituted or unsubstituted, and carboxyl.
- 20 other than R_1 , R_2 , and R_3 are not all H, and Y is selected from a natural amino acid side chain.

- 2 A method as claimed in claim 1 wherein Y is $-H_2$ (i.e. glycine "side chain").

- 3 A method as claimed in claim 1 wherein one of R_1 and R_2 is H.

- 4 A method as claimed in claim 1 wherein one of R₁ and R₂ is alkylcarbonyl (more preferably C₁-C₆ alkylcarbonyl), alkenylcarbonyl (more preferably C₂-C₆ alkenylcarbonyl), alkynylcarbonyl (more preferably C₂-C₆ alkynylcarbonyl).
- 5 A method as claimed in claim 1 wherein one of R₁ and R₂ is C₁-C₆ alkylcarbonyl and preferably methylcarbonyl (acetyl).
- 6 A method as claimed in claim 1 wherein R₃ is alkyloxy (more preferably C₁-C₆ alkyloxy), alkenyloxy (more preferably C₂-C₆ alkenyloxy), alkynyloxy (more preferably C₂-C₆ alkynyloxy) or aryloxy (more preferably phenyloxycarbonyl).
- 7 A method as claimed in claim 1 wherein R₃ is benzyloxy.
- 10 8. A method as claimed in claim 1 wherein the antimicrobial agent is penicillin or a derivative or analogue thereof or a glycopeptide.
9. A method as claimed in claim 8 wherein the antimicrobial agent is a β -lactamase-stable penicillin or a derivative or analogue thereof.
- 10 A method as claimed in claim 1 wherein the antimicrobial agent is oxacillin or vancomycin.
- 15 11. A method as claimed in claim 1 wherein the transforming agent is glycine benzyl ester, glycylglycine ethyl ester, hippuric acid, p-amino hippuric acid or propargylglycine.
- 12 The use of an agent having formula (I) of claim 1 in the manufacture of a medicament for increasing the sensitivity of a bacterial strain infecting, colonising or being carried by a patient, to an cell-wall active antimicrobial agent as described in claim 1.

- 13 A method of preventing infection and cross-infection related to carriage of a bacterial strain, comprising topical administration to the carriage site(s) of said patient, an amount of a transforming agent of formula (I) of claim 1, sufficient to render said strain more sensitive to an antimicrobial agent and administering to said patient a therapeutically effective amount of said antimicrobial agent as a co-formulant and/or co-administrant.
- 14 A method as claimed in claim 13 wherein said agent may be in admixture with one or more excipients, carriers, emulsifiers, solvents, buffers, pH regulators, flavourings, colourings, preservatives, or other commonly used additives in the field of pharmaceuticals as appropriate for the mode of administration.
- 15 A method as claimed in claim 13 wherein said agent is capable of increasing the sensitivity to the antimicrobial agent of at least one bacterial strain selected from *Staphylococcus aureus*, coagulase-negative staphylococci and enterococci, *Clostridium difficile*, and *Streptococcus pneumoniae* and other Gram-positive pathogens.
- 16 A method as claimed in claim 15 wherein the bacterial strain is resistant to the antimicrobial agent.
- 17 A method as claimed in claim 13 wherein said agent is capable of increasing the sensitivity to the antimicrobial agent of at least one of methicillin- and/or glycopeptide-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci to the antimicrobial agent to which the bacterial strain is resistant.
18. A method as claimed in claim 17 wherein the bacterial strain is resistant to at least one of methicillin and its derivatives or related antimicrobial agents; vancomycin, teicoplanin or another related glycopeptides.

19 A method as claimed in claim 13 wherein said agent is capable of increasing the sensitivity to the antimicrobial agent of at least one bacterial strain selected from *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, *Clostridium difficile*, *Streptococcus pneumoniae*, *Streptococcus pyogenes* and other streptococci and Gram-positive pathogens, where the
5 bacterial strain is causing a rapidly life-threatening infection, particularly in a debilitated host, to create 'hypersensitivity' of the infecting organisms to the antimicrobial agent.

20 A method as claimed in claim 13 wherein said agent is capable of increasing the sensitivity of EMSRA-15, -16 and/or -17, or other EMRSA, to β -lactam (and analogous) antibiotics/antimicrobial agents, and/or increasing the sensitivity of EMSRA with reduced sensitivity
10 to vancomycin, teicoplanin or other glycopeptide, or of VRSA to the aforementioned antimicrobial agents.

21 A method as claimed in claim 19 wherein sensitivity is increased to the level of a comparable non-resistant bacterial strain at a concentration of agent of 0.02M or less, more preferably 0.002M or less and most preferably 0.001M or less as determined by a standard
15 antibiotic sensitivity test.

22 A method as claimed in claim 13 wherein the antimicrobial agent to which sensitivity is increased is selected from the group consisting of β -lactam (and analogous) antibiotics/antimicrobial agent stable to staphylococcal β -lactamases), cephalosporins and glycopeptides

23 A method as claimed in claim 22 wherein the antimicrobial agent to which sensitivity is
20 increased is methicillin, flucloxacillin, cloxacillin, oxacillin, imipenam, meropenam, ceftazidime, cefuroxime, vancomycin, teicoplanin or oritavancin .

24 A method as claimed in claim 13 wherein the antimicrobial agent to which sensitivity is increased is selected from those agents that consist of a β -lactam (and analogous) antibiotics/antimicrobial agent sensitive to β -lactamases, together with a β -lactamase inhibitor or
25 a derivative or analogue thereof.

25. A method for identifying transforming agents in microorganisms of medical importance with cell walls of the structure suitable for targeting by penicillin and related/analogous antimicrobial agents and glycopeptides, wherein the composition of cross-links and mucopeptide tails in the cell wall of the target organism must be wholly or partly established, and the transforming ability of the
- 5 individual molecules with corresponding moieties selected for testing.